Authorization of animal research proposals – a comparison of harm concepts in different European regulations

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Abstract: Meeting the professional responsibilities of veterinarians in animal research has been described by the German Federal Chamber of Veterinary Surgeons (Bundestierärztekammer, BTK) as a "special ethical challenge". Veterinarians are involved in animal research, not only as researcher and animal welfare officers, but also as members of ethical review committees and as such require a unique set of skills to provide a wide range of services and practices. Animal research in Europe is strictly regulated. The harm-benefit analysis (HBA) is one of the legal corner stones in project authorization and as such has to be carried out within a specific legal framework. Hence, veterinarians (and other members of ethical review committees) require an understanding of the normative foundation of animal research legislation in order to fulfill their role and responsibilities. Against this background, it is the goal of this article (1) to introduce the rationale and role of the harm concept and the HBA in project evaluation of animal research. (2) We then outline the different harm concepts which the European and the Swiss legislation are based on and (3) elaborate on the moral significance that is given to different forms of harm within the HBA in these legal frameworks. (4) Last, we demonstrate potential practical implications of these conceptually different normative frameworks for project evaluation in animal research with the practical example of genetically disenhancing the ability of rodents to feel pain and to suffer.

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Authorization of animal research projects – a comparison of harm concepts in the Swiss Animal Welfare Act and the European Directive 2010/63/EU

Projektevaluierung im Tierversuch – ein Vergleich des Schadensprinzips zweier verschiedener gesetzlicher Regulierungen in Europa

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Summary

Meeting the professional responsibilities of veterinarians in animal research has been described by the German Federal Chamber of Veterinary Surgeons (*Bundestierärztekammer*, BTK) as a "special ethical challenge". Veterinarians are involved in animal research, not only as researcher and animal welfare officers, but also as members of ethical review committees and as such require a unique set of skills to provide a wide range of services and practices.
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Against this background, it is the goal of this article (1) to introduce the rationale and role of the harm concept and the HBA in project evaluation of animal research. (2) We then outline the different harm concepts which the European and the Swiss legislation are based on and (3) elaborate on the moral significance that is given to different forms of harm within the HBA in these legal frameworks. (4) Last, we demonstrate potential practical implications of these conceptually different normative frameworks for project evaluation in animal research with the practical example of genetically disenhancing the ability of rodents to feel pain and to suffer.

Keywords: Animal research regulation, harm-benefit analysis, regulatory ethics, animal research ethics, (non-)sentientism

Zusammenfassung

Die Erfüllung der verschiedenen beruflichen Verantwortungen von Tierärzten in der Tierversuchsforschung wurde von der Bundestierärztekammer (BTK) als „besondere ethische Herausforderung" bezeichnet. Denn Tierärzte sind in der Tierversuchsforschung nicht nur als Forscher und Tierschutzbeauftragte involviert, sondern auch als Mitglieder von Ethikkommissionen und benötigen daher eine Vielzahl von Fähigkeiten, um eine breite Palette von Dienstleistungen ausführen zu können.
Tierversuche sind in Europa strikte reguliert und die Schaden-Nutzen-Analyse (SNA) als einer der rechtlichen Eckpfeiler der Projektgenehmigung muss innerhalb eines bestimmten, vorgegebenen rechtlichen Rahmens durchgeführt werden. Tierärzte (und andere Mitglieder von Ethikkommissionen) benötigen daher ein Verständnis der normativen Grundlagen der Tierversuchsgesetzgebung, um ihre Rolle und Verantwortung adäquat erfüllen zu können.
Vor diesem Hintergrund ist es das Ziel dieses Artikels, (1) die Grundlage und Funktion des Schadenskonzepts und der SNA bei der Projektevaluierung zu erläutern. (2) Des Weiteren skizzieren wir die verschiedenen Schadenskonzepte, auf denen die europäische und die schweizerische Gesetzgebung basieren, und (3) diskutieren die moralische Bedeutung, die innerhalb dieser unterschiedlichen

rechtlichen Rahmenbedingungen den verschiedenen Arten von Belastungen in einer SNA beigemessen wird. (4) Zuletzt zeigen wir mögliche praktische Implikationen dieser konzeptionell unterschiedlichen normativen Rahmenbedingungen für die Projektevaluierung am praktischen Beispiel des *genetic disenhancements* bei Nagetieren zur Verminderung der Fähigkeit, Schmerzen zu fühlen und leiden zu können.

Schlüsselwörter: Tierversuchsregulierung, Schaden-Nutzen-Analyse, regulatorische Ethik, Ethik des Tierversuchs, (Non-)Sentientismus

Background

Veterinarians require a unique set of skills to provide a wide range of services and practices within the field of animal research for industrial, academic or official purposes. The care and keeping of laboratory animals or the experimentation, respectively, can include standard veterinary routines such as castration, vasectomy, immunization, sample collection, analgesia, anaesthesia as well as demanding surgeries, cryopreservation and assisted reproduction, which require special training.

The role of veterinarians in animal research has recently been legally strengthened by Article 25 of the European Directive 2010/63/EU (Anonymous 2013, henceforth 'Directive') which states, that "each breeder, supplier and user has a designated veterinarian with expertise in laboratory animal medicine." However, meeting the professional responsibilities of veterinarians in animal research has been described by the German Federal Chamber of Veterinary Surgeons (*Bundestierärztekammer*, BTK) as a "special ethical challenge" (Bundestierärztekammer 2017). One major challenge lies in the conflict between particular health-endangering or lethal practices for the involved animals and the veterinary professional code of conduct to prevent, relieve and cure animal diseases. The role of veterinarians as animal advocates, although from a historical point of view being a young phenomenon (Weich 2018), combined with the recent increase in moral standing of animals within society exacerbate this conflict.

The moral justification of using animals within scientific research (for the benefit to others) requires a specific moral theory, which in the case of the European Directive and Swiss Welfare Act can be found within the utilitarian tradition. The utilitarian paradigm is a perfectionist approach that tries to maximize the amount of pleasure (or interests' satisfaction) and to minimize the amount of pain (or interests' frustration) in the world. On this account, the justification of animal use in research requires a harm-benefit analysis, to justify the stress inflicted on animals by outweighing benefits (Bundestierärztekammer 2017). Having specialised knowledge about animal welfare and being involved in animal experimentation itself (preparing and performing experiments) and project evaluation (i.e. authorization in ethical review bodies), veterinarians play a crucial role in optimizing this process.

The utilitarian paradigm is compatible with professional ethics in veterinary medicine for at least two reasons. First of all, it seems to be the perfect compromise between respecting the moral status of sentient animals as well as regarding their individual interests, while still maintaining the possibility to use animals in research (i.e. by trumping their interests to achieve the "greatest good for the greatest number"). Second, it complies with most contemporary legal regulations, which play a crucial role for daily veterinary practice.

Nevertheless, the utilitarian paradigm should not be taken for granted. Animal rights theory, virtue ethics and contractarianism, the claim for stress limitation within contemporary legal frameworks (Rippe 2009, Binder 2015) or the total ban of using great apes and gibbons for animal experimentation as stated in the Austrian Animal Experiments Act (2012, §4, no. 5, lit. a) contrast the utilitarian tradition. Also, the subjective harm-concept that is presumed within utilitarianism, is not self-evident, but can be challenged by objective harm-frameworks (we elaborate on this below).

Importantly, the utilitarian framework of animal research is similar to the ethical framework applied in public health and agriculture but very different to ethical frameworks applied in veterinary practice of companion animals.

These dissents in moral theory and normative conflicts within the veterinary profession together with potential discrepancies between the veterinary professional code of conduct, personal moral convictions and given legal regulations make animal research very challenging for veterinarians. As members of ethical review committees, as animal welfare officers, or experimenters they are involved in very different roles with different responsibilities in animal research. Based on these challenges, we assume for the following, that knowledge and clarity regarding conceptual normative frameworks of the legal regulations in animal research and specific roles and responsibilities arising therefrom for veterinarians are useful to reduce moral distress.

To this end, we explain what moral theories and harm concepts the EU and Swiss regulation are based on and what practical implications follow from them.

Rationale and role of the harm concept and the HBA in project evaluation of animal research

In the following we explain the role and rationale behind animal research regulations in the EU and in Switzerland and elaborate what ethical frameworks they are based on. Ethical frameworks and principles (e.g. moral standing and harm concepts) may vary within different contexts of veterinary profession such as small animal clinic, livestock breeding, wildlife conservation or public health and thus, conceptual clarity represents a key challenge for veterinarians, professional veterinary ethics and what it means to be a good veterinarian in every field of veterinary medicine. In light of this, we think that our considerations regarding animal research should also be useful in other veterinary contexts.

The European Directive on the protection of animals used for scientific purposes demands that the intrinsic value of animals is respected and states that animal welfare is a value that is enshrined in the Treaty of the Functioning of the European Union (recital 2, 12). Similarly, the Swiss Animal Welfare Act (Tierschutzgesetz, henceforth: TSchG [Anonymous 2017]) also acknowledges that animals have a value of their own that has to be respected and that the well-being and the dignity of animals has to be protected (art. 1 TSchG).

Because of this, both the Swiss regulation and the Directive require project proposals in EU member states involving procedures on sentient animals to be approved in a review process (art. 38, Directive). For the Directive, this includes all living non-human vertebrates and cephalopods (art. 1, par. 3 lit. a, b Directive), while the Swiss legislation also includes decapods (art. 112, lit. a–d Swiss Animal Protection Ordinance; hereinafter: TSchV [Anonymous 2020]). Hence, in both, the Swiss and EU legislations project evaluation is only warranted if sentient animals are used for research purposes.

The review process of projects involving sentient animals can be divided into the evaluation of the instrumental and goal-related essentiality of a project proposal (Swiss Academies of Arts and Sciences 2017, art. 38 Directive). The instrumental essentiality evaluates the appropriateness and the necessity of the proposed experiment to achieve a specific research goal. The first evaluates to what extent the expected results are robust, reproducible and generalizable and are suitable to answer the research question, e.g. choice of best animal model, adequate operationalisation, study design and compliance with good scientific practice are evaluated. The evaluation of the necessity deals with the question if the project complies with the 3R principle (replacement, reduction, refinement), i.e. animals are only to be used if the goal cannot be achieved with non-animal means, or with cognitively less developed species, fewer animals and/or less harmful procedures.

The goal-related essentiality follows after positive evaluation of the instrumental essentiality and is considered to be a part of the ethical review of project proposals. The Directive explicitly defines seven legal purposes for the use of animals in science, e.g. basic research, translational or applied research, product safety, education and training, protection of the environment, preservation of species and forensic inquiries (art. 5 Directive). If the project complies with any of these legal purposes (art. 38, par. 1, lit. b Directive) it is then subject to a so-called harm-benefit analysis (HBA) to assess "whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical consideration and may ultimately benefit human beings, animals or the environment" (art. 38, par. 2, lit. d Directive).

This means that in case of the Directive the explicitly defined legal purposes for the use of animals for scientific purposes and their pertaining interests for humans, animals and the environment are weighed against the inflicted harm on animals.

The Swiss Animal Welfare Act stresses the "inherent worth of the animal" and experiments are only legally admissible if they serve one of the following „legitimate interests of society", e.g. preservation or protection of the life and health of human beings or animals; new knowledge concerning fundamental biological processes or protection of the natural environment (art. 137 par. 1, lit. a–c TSchV). Further it is stated: "If any stress imposed on the animal cannot be justified by overriding legitimate interests, this constitutes a disregard for the animal's dignity. Stress is deemed to be present in particular if pain, suffering or harm is inflicted on the animal, if it is exposed to anxiety or humiliation, if there is major interference with its appearance or its abilities or if it is excessively instrumentalised" (art. 3, lit. a TSchG).

This means that in the case of the Swiss Animal Welfare Act "legitimate interests of society" (Swiss Academies of Arts and Sciences 2005) are weighed against the harms of the animals and their dignity, which "is not duly respected if they are subjected to harms that cannot be justified by preponderant interests" (Swiss Academies of Arts and Sciences 2005).

Together, this shows that the assessment of the goal-related essentiality evaluates in both legislations whether the goal of the project is important enough to justify harms in animals which is only the case if the expected benefit outweighs the harms on animals.

Against this background, it becomes clear that the weighing of human interests against animal harms requires a clear understanding of harm and benefit and how they are to be weighed. What can legally be considered as harm, depends on the normative framework the Directive and the Swiss Animal Welfare Act are based on. To this end, we outline the harm concepts the European and the Swiss legislation are based on. We examine what is considered as harm and (3) elaborate on the moral significance that is given to different forms of harm within the HBA in these frameworks. (4) Last, we discuss potential practical implications of these different normative frameworks for project evaluation in animal research with the practical example of genetically disenhancing the ability of rodents to feel pain and to suffer.

Sentientist and non-sentientist harm concepts in the European and the Swiss regulation

A crucial role in our argumentation plays the distinction between sentientist and non-sentientist harms. Here we follow Klaus Peter Rippe (2008), who defines sentientist harms as subjective, negatively experienced mental states (i.e. "subjective harms"). Importantly, when using the word sentientist we do not refer to the moral status of a being (e.g. anthropocentrism, sentientism, biocentrism), but refer to a specific harm concept. In contrast non-sentientist harms include harms that do not cause negative subjective experience for the affected individual. In general, non-sentientist harm concepts can be found in biocentrism, who morally considers all living beings, not only sentient beings (e.g. Taylor 1989, Rutgers and Heeger 1999). In biocentrism the precondition for harm is not sentience, but having a species-specific "good of its own", i.e. this means that every being that can flourish, e.g. grow, maintain and reproduce itself, can be harmed. Because non-sentient forms of harm are not necessarily connected to a subjective, negative experience, they are also referred to as "objective harms". Sentientist harm concepts are paradigmatically found in pathocentrism, where only sentient beings have a moral status, although some pathocentrists also include non-sentientist harms as morally relevant (e.g. Regan [2004] 1983, Wolf 2014).

The EU Directive is predominantly based on consequentialistic moral theory, with a hierarchic pathocentrism. The importance of pathocentrism is shown by the fact that only sentient beings are protected by the legislation (moral status) and its focus on negative subjective experiences of animals (e.g. pain, suffering and distress) (Grimm 2015) and therefore on a sentientist harm concept.

However, there are at least two exceptions of non-sentientist forms of harm that are also considered, e.g. "prevention from expressing natural behaviour including restrictions on the housing, husbandry and care standards" and the "breeding genetically altered animals which are expected to have no clinically detectable adverse phenotype" (Annex VIII Directive).

Both mentioned examples are classified as „mild" pain, distress and suffering. Of note, within procedures classified as more harmful than „mild" (e.g. moderate or severe) only sentientist forms of harm can be found. This shows that although non-sentientist forms of harm are considered in the Directive, they only play a minor role compared to sentientist forms of harm.

The Swiss Animal Welfare Act also acknowledges that sentientisic forms of harm (orig. "Belastungen") such as pain, suffering and anxiety, have to be taken into consideration within a HBA. Importantly, the Swiss TSchG also considers non-sentientist harms defined as "major interference with animal's appearance or abilities, humiliation and excessive instrumentalisation" (Camenzind 2013). They are considered non-sentient (or objective harms) because they do not lead necessarily to negative subjective experiences for the individual. Examples include, e.g. glowfish (appearance), dehorned cows (appearance and abilities) or ridiculing animals with funny costumes (humiliation), etc. Below we discuss how important these non-sentient forms of harm are for project evaluation within the Swiss regulation.

The moral significance of harm within the HBA

So far, we have primarily reflected on a conceptual level what is considered to be harm in the Directive and the TSchG. In the following we will discuss how much moral significance is given to different forms of harm within the HBA in the Swiss and EU regulation.

To understand the difference between sentientist and non-sentientist harms in the Swiss regulation, one has to relate them to the ethical theory the regulation is based on. On the constitutional level the dignity of creature ("Würde der Kreatur") has been incorporated in 1992. In Article 120 of the Swiss constitution on non-human gene technology it is stated that the dignity of all living beings has to be taken into account. The dignity of creature is a concept with a biocentric view of moral status, and as such, it also includes non-sentient beings, like plants and other less complex organisms. Against this biocentric background on the constitutional level, it becomes apparent that harm in the form of "major interference with its appearance or its abilities", "humiliation" and "excessive instrumentalisation" found in the TSchG do not have to be experienced negatively to be legally relevant within the HBA and thus, major interference with animal's appearance or abilities, humiliation, and excessive instrumentalisation can potentially affect the decision-making process in project evaluation.

Interestingly, only sentient organisms are protected by the Animal Welfare Act in Switzerland. However, from a philosophical point of view, there is, according to biocentrism, no objective standpoint, from which the flourishing of one organism can be regarded as being more valuable than the flourishing of another organism (Taylor 1989) and thus the TSchG has been criticized for its exclusion of non-sentient animals (EKAH 2001).

On the practical level, both regulations are very similar in terms of how the evaluation process is operationalised, e.g. the evaluation of the instrumental and goal-related essentiality (HBA). However, due to the differences regarding their underlying harm concept, i.e. the role and significance of non-sentientist, objective forms of harm, different harms have to be taken into consideration in the HBA within both regulations. In the following we will analyse how the inclusion of non-sentient concerns regarding major interference on appearance and abilities, humiliation, dignity and excessive instrumentalisation can potentially affect project evaluation. To illustrate this, we will use the genetic disenhancement of rodents (i.e. the genetic reduction of their ability to feel pain and to suffer) as practical example.

Implications for project evaluation

The responsibility of carrying out project evaluations lies with competent authorities. Competent authorities are often supported by ethical review committees whose composition can be largely diverse, e.g. various members can have a very heterogeneous background and expertise, e.g. scientific research, veterinary/animal welfare, NGOs, lay people, etc. (Olsson et al. 2016). Ultimately, these committees advise competent authorities to decide whether the instrumental and goal-related essentiality is met. The principle of legality in constitutional states requires authorities to come to decisions on legal questions in compliance with explicit legal rules (Grimm 2015). This results in specific responsibilities (i.e. what they have to consider) and limitations (i.e. what they are not allowed to consider) in their decision-making process, i.e. the authorization (or rejection) of research proposals must only be based on and is necessarily limited to the normative framework of the legal regulations, e.g. Directive/2010/63/EU (for all EU member states) and the Swiss regulation for project evaluation in Switzerland. This means that authorities and committees working under the EU Directive or Swiss regulation are to interpret „ethical considerations", "harm", "overriding interests" and "excessive instrumentalisation", respectively with regards to implicit and explicit normative criteria their legal regulations are based on. To illustrate the importance of this for project evaluation, we will now discuss how the different normative frameworks can potentially affect project evaluation. To this end, we will use the genetic disenhancement of rodents to reduce their ability to feel pain and to suffer as a practical example.

Genetic Disenhancement of rodents

The Directive acknowledges the "intrinsic value" of animals and is concerned with animal suffering and thus it requires procedures to be performed with the least possible suffering. In order to minimize animal suffering,

different strategies have been pursued. Paul Thompson coined the term "animal disenhancement" for alterations of animals to better suit their environment (Thompson 2008, D'eath et al. 2010). Recent progress in pain research (i.e. unpleasant sensory experience [sensation], which leads to physiological changes and/or behavioural responses designed to escape or avoid the negative experience [Federal Food Safety and Veterinary Office 2017]) could show that pain can be divided into two distinct dimensions that correlate to activity in different brain regions (Farah 2009, Price 2000, Rainville et al. 1997). On the one hand, the sensory dimension of pain is associated with the primary and somatosensory cortex and constitutes the quality of the pain (i.e. constitutes the localisation, intensity and duration of pain), its localisation and intensity. On the other hand, the affective dimension of pain is associated with the anterior cingulate cortex and the insula cortex. Several studies show that this area is relevant for the negative perception of pain, i.e. how the pain is recognised, how much one minds the pain or how unpleasant the pain is (Farah 2009, Rose 2002, Shriver 2006). Importantly, it has been demonstrated that one can genetically modify the affective dimension of pain independently of the sensory dimension (Rainville et al. 1997). This means that it might be possible to genetically reduce the affective (subjective and painful) dimension of pain (Shriver 2009) and/or chronic pain symptoms, while leaving the acute pain response intact (Wei et al. 2002).

The recent advances in gene editing and the understanding of the molecular processes underlying pain physiology, might provide a way to potentially genetically reduce or eliminate research animal's ability to feel pain (as something negative) (Shriver 2009, Price 2000, Rainville et al. 1997).

Rodents are the most used species in animal research (Anonymous 2008, Taylor et al. 2008), and relatively easy to genetically manipulate. Assuming (speculatively) that it might be possible to genetically eliminate research animal's ability to feel pain, and assuming that genetically disenhanced animals behave "normal" compared to their genetically unaltered counterparts, the suffering of millions of research animals every year could be reduced.

Prima facie, the reduction of pain and suffering (sentient, subjective harm) would be a strong argument in favour of genetic disenhancement within a sentientist and consequentialist framework. But is it that simple? In the remainder of this paper, we will evaluate the implications of our thought experiment for project evaluation within the framework of the Directive and the Swiss Animal Welfare Act.

Implications for project evaluation within the EU Directive

Within the EU Directive harms have to be weighed against potential benefits "taking ethical considerations" into account. When doing so, authorities are only allowed to base their decision on arguments that are compliant with consequentialist moral theory that includes a hierarchical pathocentrism based on anthroporelational criteria (explained above).

Under the assumption that pain and suffering would be reduced, genetic disenhancement seems, *prima facie*, to be in compliance with "refine" of the 3Rs, without necessarily affecting the number of animals (reduce) and/or the species used (replace). Also, since the amount of harm that needs to be outweighed is greatly reduced it should dramatically facilitate the HBA (goal-related essentiality). Thus, from the normative standpoint of the European Directive there seems to be no objection to the practice of genetically disenhancing rodents in principle. But secondary factors may also have to be taken into consideration.

However, a plethora of objections have been raised against genetic disenhancement. Opponents have raised the concern that from a practical perspective the unpredictability of the concrete effects of the genetic manipulation are relevant (Ferrari 2012, Macer 1989). Pain is a complex phenomenon with many dimensions, e.g. physical, sensory, behavioural, emotional, cognitive. It remains to be examined, how pain elimination affects the organism as whole, e.g. perception of positive experiences, animal health or empathy. Rodents are social animals and thus it should be taken into consideration that the elimination of the affective pain dimension could potentially influence the social behaviour of the animals, e.g. emotional contagion or conciliation behaviour (Bekoff and Pierce 2009). Depending on how the social behaviour is affected, this could represent sentient as well as non-sentient harm, e.g. negative effects on the caring behaviour of a mother towards her offspring would represent a sentient harm, if the mother does not care for the offspring anymore. At the same time this could lead to non-sentient form of harm due to the negative effect on species-specific behaviour. However, this is a speculative claim, which due to a lack of empirical data, is difficult to prove. The actual consequences of genetic disenhancement can only be analysed within a retrospective evaluation.

Another objection might be that erasing an animal's ability to feel pain and to suffer turns a sentient being into a non-sentient being, which would potentially be against the requirement of the Directive that "animals should always be treated as sentient creatures" (recital 12, Directive). However, we do not think that the inability to feel pain and suffering means that animals can no longer have other emotions, i.e. even if the ability to feel pain and to suffer is missing, animals would still be able to experience positive emotions and thus, would still be sentient beings, although it is not known yet how pain elimination affects other sensations. In case the genetic disenhancement would in fact turn animals into non-sentient beings, the regulations of the Directive would no longer apply to them.

Most of these objections concern sentientist forms of harm. As we have explained above, objective harms are also part of the Directive but only play a minor role (e.g. "prevention from expressing natural behaviour including restrictions on the housing, husbandry and care standards" and "breeding genetically altered animals which are expected to have no clinically detectable adverse phenotype" [Annex VIII, Directive] are classified as mild harms).

Based on the above, it seems, *prima facie*, that within the normative framework of the Directive, mild (objective) and unknown and hypothetical (subjective) harms potentially generated by genetic disenhancement would probably be outweighed (in a HBA) by the reduction of obvious and certain (subjective) pain, suffering and distress (caused by experiments), which are considered more important in the Directive.

Thus, with regards to the European Directive (and within a sentientist and consequentialistic point of view), *prima facie*, there seems to be no strong objections to genetic disenhancement of rodents.

Implications for project evaluation within the Swiss regulation

As we have seen, genetic modifications of research animals are a polarizing topic and controversially discussed. The Swiss legislation with its inclusion of animal's dignity and the importance given to non-sentientist forms of harm within that framework might to some extent provide an answer as to why this is the case.

In the following we will discuss whether the non-sentientist harms and their significance given to in the Swiss regulation (e.g. major interference with the appearance or abilities of animals, humiliation and excessive instrumentalisation and the concept of animal dignity) (Camenzind 2013, art. 3 TSchG), allow for other objections (compared to the Directive) to be considered in project evaluation.

The purpose of the TSchG (art. 1) is to protect the dignity and welfare of animals. This means that the well-being of animals is not limited to sentientist forms of harm, but it also includes a non-sentientist harm dimension, which is explicitly mentioned in article 3 of the Swiss Animal Welfare Act:

„[...] If any stress imposed on the animal cannot be justified by overriding interests, this constitutes a disregard for the animal's dignity. Stress is deemed to be present in particular if pain, suffering or harm is inflicted on the animal, if it is exposed to anxiety or humiliation, if there is major interference with its appearance or its abilities or if it is excessively instrumentalised".

In the case of genetically erasing the animal's ability to feel pain and to suffer the appearance of the animal is not changed. However, genetic disenhancement represents a major interference with animal's abilities, defined as a long-term or irreversible alteration of species-specific capacities or biological functions (Federal Food Safety and Veterinary Office [FSVO] 2017). Also, according to TSchG the "species-appropriate behaviour within the limits of their biological adaptability" is important for their well-being (art. 3 lit. b, par. 2 TSchG). This raises the concern, how genetic disenhancement interferes with species-appropriate behaviour (see above par. 5.1).

"Humiliation" (Bolliger 2016) is usually understood as ridiculing an animal (e.g. by dressing animals up in costumes or demanding submissive behaviour), which in the case of genetic disenhancement is not the case.

"Instrumentalisation" can be understood as a "four element" relation: someone (agent) uses an entity (means) in a specific way (mode) for a particular purpose (Camenzind 2019). Regarding animal experimentation in general and animal disenhancement in particular it is obvious that animals are instrumentalised by researchers. Animals are bred to function as model animal in research, e.g. to generate knowledge, drugs, therapies, etc. According to the TSchG different modes of instrumentalisation can be distinguished. To instrumentalise animals moderately is legally permitted, e.g. studying the behaviour of wild animals. In contrast, excessive instrumentalisation refers to modes of instrumentalisation, which possess a certain quality, intensity or duration that require a justification, i.e. this means that the action as such is not necessarily impermissible, but it requires specific legally permitted benefits to be at stake to justify the excessive instrumentalisation, e.g. a demonstration in a HBA that the "stress imposed on the animal" can be „justified by overriding interests" (see below).

What it means to instrumentalise an animal excessively can be explained on a value related dimension and on a content related dimension. The value dimension refers to a disrespectful attitude of the agent, while the content dimension refers to a disrespectful action (Hauskeller 2007). Since the dignity of animals is based on their inherent worth, animals are instrumentalised excessively, if their inherent worth is not recognized, not respected or if the necessary condition of their good of their own is eradicated. This is the case, if animals are reduced to their aesthetic, social or instrumental value, and therefore merely or excessively to their usefulness for someone.

This explanation on the value related dimension is not yet sufficient to analyse if animal disenhancement instrumentalises animals excessively – it only provides an explanation on a formal level, why certain actions require moral and legal justification. Therefore, the conceptual value dimension has to be translated to the practical content related dimension and the animal's flourishing. On the content related dimension, the context of the action, in our case the disenhancement, is also important. As already mentioned disenhanced animals are bred to serve human beings as research models etc., which infringes the animal's flourishing. Also, animals are kept in captivity and most animal experiments result in the death of the animal. Hence, their flourishing is restricted and prematurely terminated by force and thus, the animals' good of their own is not respected properly. The infringement on the animals' flourishing caused by their captivity and their premature death has to be justified by overriding interests.

Because pain and suffering are negative experiences, it seems morally desirable from a sentientist perspective to avoid animal pain and suffering. However, from a perspective that is concerned with animal flourishing (beyond negative subjective experiences) the reduction of pain sensitivity might only be morally relevant, if it negatively affects animal flourishing. Importantly, although pain is a negative experience, this does not mean that pain only has negative effects on flourishing (Melzack 1996, 11f.). Pain also has a survival function since pain occurs before a serious injury happens (e.g. hand on a hot stove). Also, painful experiences prevent further injuries by learning to avoid dangerous objects or situations, and pain limits activities to recover more rapidly. The elimination of pain thus eliminates an important physiological mechanism to cope with different threats and to guarantee flourishing.

Interestingly, studies have shown that eliminating the affective pain dimension can leave acute pain features and acute responses to noxious stimuli intact (Shriver 2009). Thus, animals are likely to still exhibit normal guarding behaviour (i.e. behaviour aimed at avoiding pain), making an increase in self-injuries unlikely.

To summarize, genetic disenhancement represents an excessive instrumentalisation of animals because it infringes with animal flourishing.

However, as already mentioned above, the peculiarity of the Swiss dignity concept is, that even if the dignity of an animal is negatively affected, i.e. due to non-sentientist harms such as major interference with animal's

abilities and excessive instrumentalisation, they can be legally justified within an HBA. If the legally legitimate interests of society outweigh the inflicted harms on animals then the dignity of animals is still regarded and thus the project legally permitted. If the involved harms ca not be justified by overriding interests, animal dignity is disregarded and the project would need to be rejected.

Conclusion

We have compared the normative framework of Directive 2010/63/EU and the Swiss regulation with regards to project evaluation in animal research. We have explained that committee members are bound to the principle of legality, i.e. committee members are limited in their decision-making by the boundaries of the law. In the case of Directive 2010/63/EU this means that committees, when "taking ethical consideration" into account in their evaluation of the goal-related essentiality of project proposals, are almost exclusively allowed to base their decision on a sentientist harm concept and consequentialistic moral theory. Within this framework, harm is primarily understood as sentientist forms of harm, i.e. pain, suffering and distress experienced as negative subjective sensations, while non-sentientist (objective) forms of harm, which do not lead to negative subjective experiences for the animal only play a minor role.

Authorities working under the Swiss regulation are required to base their decision on a biocentric normative framework. The Swiss regulation considers the same sentient forms of harm as the Directive, while it also includes and gives significant importance to non-sentient forms of harm, e.g. major interference with the appearance and the abilities of animals and excessive instrumentalisation in project evaluation. The conceptual differences underlying the respective harm concepts of the regulations have important practical implications for project evaluation – while projects within the EU framework (almost exclusively) have to demonstrate in a HBA that the sentientist (subjective) harm on animals is outweighed, projects in Switzerland also need to be able to demonstrate that their potential benefits can outweigh not only the sentientist but also the non-sentientist harms on animals.

Since sentientist forms of harm would be greatly reduced by genetic disenhancement, we have come to the conclusion that regarding the harm framework of the Directive there are, *prima facie*, no strong objections to such actions. For the Swiss regulation, we conclude that genetic disenhancement represents an excessive instrumentalisation and a major intervention in the abilities of the animal. However, these non-sentientist forms of harm can potentially be justified if other overriding interests outweigh these forms of stress within a HBA.The analysis provided shows that genetic disenhancement requires justification by HBA in both frameworks. While the Directive almost exclusively regards sentientist forms of harm the inclusion (and the moral significance given) to non-sentientist forms of harm such as excessive instrumentalisation and major interference with appearance and abilities and violation of dignity found in the Swiss regulation considerably raise the bar for a positive project evaluation compared to the EU Directive.

Discussion and outlook

In this paper, we evaluated whether genetic disenhancement complies with the Swiss and EU regulations, focusing our argumentation on the evaluation of the different harm concepts these regulations are based on. Besides passing a harm-benefit analysis, researchers in their project proposals also need to demonstrate that their goal falls under a legal purpose for the use of animals for scientific purposes, i.e. it needs to be evaluated whether genetic disenhancement with the goal of "refinement" is a legally legitimate interest as stated in article 8 (par. 2, lit. a–e) of the Federal Act on Non-Human Gene Technology (Anonymous 2018) and article 5 of the Directive (Anonymous 2013), respectively. The "legitimate interests of society" within the Swiss regulation include human and animal health; guaranteeing food security, the reduction of harm caused to the environment, the preservation and improvement of environmental conditions, securing a substantial economic, social or environmental benefit for society and increasing knowledge and the interests. And further article 9 of the Federal Act on Non-Human Gene Technology (Anonymous 2018) states, that "genetically modified vertebrates may only be produced and put into circulation for purposes of research, therapy, or diagnostics in human or veterinary medicine". The Directive states seven legal purposes for the use of animal in research, e.g. basic research, translational or applied research, product safety, education and training, protection of the environment, preservation of species and forensic inquiries (art. 5 Directive). Based on these legal interests and legal purposes it is, at least not *prima facie*, clear that "refinement" for refinement's sake is a legally sufficient purpose for the use of animals in research for the Directive and within the Swiss legal framework. This is also demonstrated by a recent case in Switzerland, where a project proposal at the Swiss Federal Institute of Technology (ETH) in Zurich with the goal to quantify the stress levels of zebra finches due to head-fixing was rejected on the basis that studies solely aimed at improving future studies were unwarranted (Anonymous 2019). This ruling, at least so far, seems to be an exception, but it indicates that the decision on whether "refinement" is a legal purpose is not clear-cut.

Notwithstanding that genetic disenhancement of research animals might be admissible within both the EU Directive and the Swiss regulation, there are important conceptual differences regarding the harm concept between these normative frameworks. That these conceptual differences might indeed have practical implications is (at least) indicated in the following two court decisions. First, in Bremen, Germany, in 2012 a court decision rejected to renew Andreas Kreiter's licence to work on macaques because his work was „too far from application" (Abbott 2010) and because"it is ethically not justifiable to inflict this kind of pain on animals for the generation of neurobiological basic knowledge" (Anonymous 2012). After a long legal dispute, however, the decision was successfully appealed by Kreiter at the highest court in Germany (*Bundesverwaltungsgericht*) (Anonymous 2014). The court ruled that the"licensing authority does not have discretion in its decision" and that „the burden on the experimental animals (rhesus monkeys) is ethical in view of the high scientific significance of the project" (Anonymous 2014, translation of ours).

A similar case happened in 2006 when the authorities in Zurich declined to renew Kevan Martin's licence for primate work (Abbott 2010). The authorities ruled that Martin's work offended the dignity of the animals and would not generate practical benefits in the foreseeable future. Unlike in Germany, Switzerland's Supreme Court upheld the decision (Abbott 2010). The fact that the court in its verdict explicitly referred to the dignity of the animals implies that the non-sentient concepts of harm, in practice, can play an important role in project evaluation in Switzerland.

We have mentioned that veterinarians in their role as members of ethical review committees, as animal welfare officers, or experimenters are legally required to comply with legal animal research regulations, that are based on different harm concepts (sentientist vs. non-sentientist harms).

However, the field of veterinary practice includes a wide variety of different contexts, such as companion animals, small animal clinic, agriculture, conservation medicine, wildlife management or public health, whose practices are also based on different legal and theoretical frameworks e.g. regarding animal welfare, animal suffering, moral significance of animals, but also harm concepts. The importance of non-sentient harms become apparent in the discussion whether veterinarians should apply artificial insemination of British bulldogs because of extreme breed characteristics (they cannot reproduce independently which some consider a harm) or in the critique on dehorning cows, which by opponents is considered a major interference with the appearance of the animal.

The different moral significance given to animals and sentientist and non-sentientist harm in different contexts demonstrates how multi-layered, complex, diverse and unstable veterinary practice (and ethics in veterinary practice) in different contexts is. In light of this it becomes evident that conceptual clarity regarding the roles and responsibilities within a specific given context represents a key challenge for veterinary profession and professional ethics in veterinary practice. The elaboration and clarification on the normative frameworks of the legal regulations of animal research in Switzerland and the EU and the specific roles and responsibilities that follow from them should help veterinarians with regards to better understanding veterinary professional ethics and context-sensitive roles and responsibilities in veterinary practice. Conceptual and terminological clarity do not solve the diverse moral dilemmas veterinarians are facing. However, they provide a better understanding of different sources of moral conflicts and act as a tool to cope with them, thus hopefully helping to reduce moral distress in veterinarians.

Conflict of interest

The authors declare that they do not have any conflicts of interest.

Ethical Approval

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